# Feedback Medicine: Control Systems Concepts in Personalised, Predictive Medicine and Combinatorial Intervention

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## Introduction

In its broadest definition, systems biology is the application of a 'systems' way of thinking about and doing cell biology [1]. By implication, this also invites us to consider a systems approach in the context of medicine and the treatment of disease. In particular, the idea that systems biology can form the basis of a personalised, predictive medicine [2, 3] will require that much closer attention is paid to the analytic properties of the feedback loops which will be set up by a personalised approach to healthcare. To emphasize the role that feedback theory will play in understanding personalised medicine, we use the term *feedback medicine* to describe the issues outlined in these working notes.

More generally and beyond the personalised medicine debate, we advocate this 'systems' approach be extended to medicine as an important ingredient in future bio-medical research. In this context, and in our interpretation, the systems approach pays close attention to:

1. Quantitative Modelling. Traditionally, due to the difficulty of obtaining quantitative data, biological models have been qualitative and descriptive rather than quantitative and predictive. In systems biology, we seek to utilise emerging advances in sensing and analysis to generate and use quantitative models. Apart from the obvious benefits of permitting predictive *in silico* modelling of biological system behaviour, there is also the potential for using more powerful statistical tools in modelling, hypothesis testing, and parameter estimation to be applied. However, for this potential to be realised data records will be required that are much longer than currently available, collected using consistent and repeatable measurement protocols, and with appropriate sampling rates. These three issues are enormously important and, given the current status of bio-sensing and data collection, they represent correspondingly enormous challenges to bio-sensing for systems biology.

2. System Dynamics. The transients, long term trends and steady state behaviour of a biological system are all key components in understanding the behaviour of a biological system. Steady state behaviour alone is inadequate in many cases to give the detailed knowledge of system response required for modern medicine and surgery[1].

3. Feedback and Interactions. The well known interconnections of components in feedback, feedforward, nested systems and other combinations are important elements in understanding the behaviour of an entire system based on the interaction of it's constituent parts [4, 5].

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[1]The healing processes after surgical intervention are all based to some degree or another on an assumed biological mechanism for self-repair within organisms. By building models of the dynamics of these mechanisms it is possible that systems biologists may assist the development of surgical practice.

We note that this systems approach has its roots in the analysis of dynamical systems, and thus differs substantially from the bioinformatics perspective, which being grounded in computer science focusses on data characterisation through pattern recognition, correlation analysis, clustering and classification. bioinformatics is an important way of developing quantitative statements of the components in biology or processes that have achieved steady state. However, one of the roles of system dynamics and feedback theory in systems biology is to provide a very distinct paradigm whereby we can *analyse and understand* the *dynamical* behaviour of organisms. Thus bioinformatics and systems biology perform complementary roles that will increasingly overlap as their synergies develop.

In these notes we consider feedback and control systems concepts applied to two important themes in medical systems biology - personalised medicine [2] and combinatorial intervention [6]. In particular, we formulate a feedback control interpretation for the administration of medicine, and relate them to various forms of medical treatment. There are two reasons for doing this. First, *personalised medicine* implies a tailoring of measurement, analysis of condition, diagnosis and treatment to individual needs, that closely mirrors the processes within a feedback control system. Second, the notions of *combinatorial* action [7] in treatment clearly indicate that the processes of medicine are, in the terminology of control systems theory, multivariable and coordinated in nature. For this reason we will use the term *coordinated*, in place of the phraseology connectivity and combinatorial.

Personalised medicine implies a significant shift from what might be termed population–based medical research, where the emphasis is on determining how the population behaves on average. Instead, this kind of information will be merged with information on how a specific individual responds to various kinds of treatments. For this to be viable, several ingredients may be needed such as:

- More regular monitoring, including self monitoring, of important diagnostic indicators;

- Enhanced tools for learning appropriate individual information from time trends of individual diagnostic indicators;

- The need for treatment regimes and recipes that are widely applicable and give good clinical results for a variety of individuals with diverse steady state and dynamic responses to the same treatment[2].

Note that personalised medicine has often been discussed in relation to *pharmacogenetics* (see for example [3]). Our approach differs to this approach in that we place a much higher emphasis on the role of dynamic variables (such as concentrations of proteins and other variables) than on the more static system parameters (e.g. genomic data) typical of pharmacogenetics. Whilst some of the current difficulties of implementing pharmacogenetics are shared by our approach to personalised medicine, the role of dynamics in prediction and regulation we believe to be an important ingredient dictated by a systems biology approach.

In designing the enhanced tools and treatment regimes noted above we believe that the tools of feedback theory are of potential value. Biological processes are nonlinear, time-varying systems, and in this form control theory is hard to apply. However, using linearised stationary models, useful things can be said using multivariable feedback system theory. In particular, multivariable systems are known to have many special and subtle features which have been exhaustively studied by control theorists, and there is a large and informative literature on the subject (see e.g. [8]). Thus the objective of these notes is to explore ways in which ideas from linear feedback theory and practice might assist in the overall design of personalised medicine and combinatorial intervention.

Our motivation in beginning this exercise now is the observation that the technologies for automatically measuring the condition of a patient are advancing rapidly. Thus it is both timely and necessary to consider how feedback control ideas could help diagnosis, treatment design and administration to be systematically integrated with automated processes of measurement within the *personalised medicine* framework. A further hope is that this systems approach may also clarify and give technical basis for strategies adopted in some traditional approaches to medicine. To reiterate our earlier remark we emphasise the central role of feedback mechanisms in disease treatment as a whole by refering to its study as *feedback medicine*.

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[2]In the feedback control systems literature this is known as 'robust control' where a feedback controller achieves good performance for a whole class of different 'plants' to be controlled.

# 1 The Systems Setup

In this set of notes, we will not discuss specific scientific evidence for the model framework proposed. However, our (limited) understanding of the literature is that the framework we use may be of interest and is consistent with that implied in [2, 6]. The model framework we propose here has two known limitations:

- Our model here assumes no real "intelligence" or significant dynamics in disease effects, and therefore the results here may well be inapplicable (at least in their current form) to the treatment of infectious diseases (e.g. viral or bacterial). In such cases, the disease itself may well show elements of adaptive behaviour and this may be crucial in the design of anti-bacterial or anti-viral therapies.

- We do not directly address here the differences between Homeostasis and recent work on Allostasis (e.g. [9]). We note that the difference in these viewpoints, whilst potentially important from a medical viewpoint, does not significantly alter the discussions contained here. Homeostasis can be considered, within a control systems framework, as a *regulation problem*, whereas Allostasis resembles the *servo* or *setpoint tracking problem*[3].
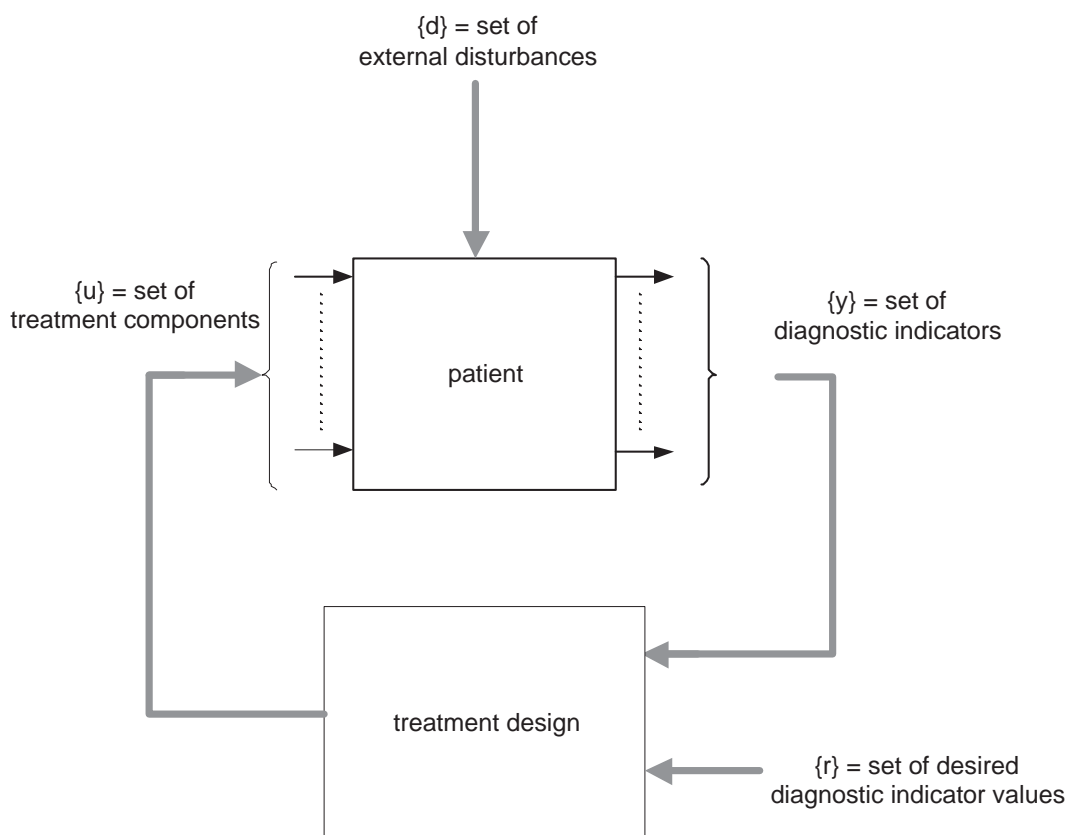


Figure 1: A feedback control interpretation for treatment of disease.

In a general form, Figure 1 shows a feedback systems representation of the disease treatment process in a way that mimics the actions of a physician. In context of this figure treatment design includes diagnosis, selection of treatments, and potentially the design of individual treatments. Before going

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[3]The function of a regulatory feedback controller is to maintain a system output at a specified level (e.g Homeostasis), while a tracking or servo feedback controller is designed such that the output tracks changes in some reference variable which is defined externally to the feedback loop (e.g. Allostasis).

into the specifics of each of these, it will be useful to introduce some systems terminology and seek out biological parallels.

## 1.1 Dynamic Variable Definitions

**Diagnostic Indicators (y):** In Figure 1 the state of health of a patient is determined indirectly by a set of 'diagnostic indicators', $\{\mathbf{y}\}$ which are a set of measurements, that change with time, and that when taken together indicate the patient's response to some treatment and/or their state of health. In control systems terminology, $\mathbf{y}$ is a vector valued function of time, often referred to as the *output*.

**Reference levels for Diagnostic Indicators (r):** In the block 'treatment design' the diagnostic indicators $\{\mathbf{y}\}$ are compared with the desired (or *reference*) diagnostic indicators denoted by $\{\mathbf{r}\}$. Note that it would not be uncommon for there to be a range of acceptable values for the diagnostic indicators, in other words, perfect tracking of $\mathbf{y}$ to $\mathbf{r}$ is not required. $\mathbf{r}$ is often called an 'exogenous' input, since this variable is typically predefined based on relevant medical research.

Each member of the set $\{\mathbf{r}\}$ will comprise a set of permissable values corresponding to the range of values that might be anticipated in a healthy person of the class being considered. Currently, these consist of a set of indicators that are learnt by physicians as part of their training. No one physician has a mastery of all possible indicators and the set of known indicators is incomplete – being constrained by measurement technology and the boundaries of medical knowledge.

**Treatment Components (u):** The treatment components are largely at the disposal of the physician and patient where timing and dosage of a range of different treatments (e.g. drugs) can be applied. In control systems terminology, $\mathbf{u}$ denotes the vector of inputs (as a function of time), which need to be specified as a function of the historical and current values of $\mathbf{r}$ and $\mathbf{y}$. An expanded discussion of how we think of treatment components is given later in Subsection 1.4.

**Disturbances (d):** The disturbances denote another set of variables $\{\mathbf{d}\}$, often not measurable, that are not under direct control of the patient or doctor, but which have a significant effect on the patient, and the diagnostic indicators. For example, stress, food, toxins might all be considered as possible system disturbances. In control systems terminology, these are often described as 'exogenous disturbances'.

## 1.2 Internal Variables: States and Model Parameters

The variables described above in Subsection 1.1 are all variables that are either external to the patient, or can be measured externally. Usually these external variables provide only an incomplete indication of the underlying physiological condition of the patient. To complete the picture and to allow prediction of future output values, two further sets of variables are used in dynamic systems theory. The first of these are *Model Parameters* that show little or no dynamic variation, but are needed to define in a quantitative way the model behaviour. Examples of model parameters in biological systems are things such as the relevant components of an individual's genomic data, reaction rate constants, decay rates, diffusion constants etc. Some of these may be difficult to determine in biological systems from first principles, with only qualitative information being available. Where they can be quantified however it may be that real time measurements together with system identification techniques can be used to find numerical values for model parameters.

The second set of important internal variables is the state vector. In dynamical systems theory the state $\{\mathbf{x}\}$ completely and independently describes the current status of a system and when taken with an appropriate mathematical model (including values for all parameters) of the system, and specification of all future inputs and disturbances, completely specifies the future behaviour of the system [10]. In other words the state $\{\mathbf{x}\}$ is central to the ability to predict a system's behaviour – a point that has great relevance to in our interpretation of predictive medicine as outlined in [2].

The concept of system state is extremely powerful and accordingly it occupies a central role in the theory and analysis of dynamical systems. The ways of determining a complete and independent set of states for systems made up of inanimate objects is well understood [11], but this is not true in the case of living organisms. An important question in the systems approach to biology and medicine is therefore: Does an analogous concept of state exist in biology and medicine? We suggest that if the central dogma

of biology holds true, then the set of concentrations of all proteins synthesised by an organism is a natural candidate for the state $\{\mathbf{x}\}$ of that organism.

We can put this in diagrammatic form in Figure 2 where we indicate how the patient might be represented, in general terms, in a feedback systems formulation. While this figure is meant only to be illustrative it shows how the different aspects of medicine might be approached from a systems viewpoint. First note that the treatment set $\{\mathbf{u}\}$ corresponds in feedback control terms to a set of actuation signals. By analogy we suppose that the treatment reaches the central state generating mechanism – which produces the set of proteins – via a form of biological actuation mechanism. The task of the treatment designer is to understand the actuation mechanism sufficiently to ensure that the treatment produces the desired affect on the patient state. Typically, this desired affect is to correct a particular part of the state which has deviated significantly from it's desired concentration, without disturbing other parts of the state that are already at appropriate levels.

Note also the role of the block labelled 'sensing mechanism'. This produces measurements that form the diagnostic indicators, or outputs, as some combination of the states or subset of the states. In physical systems this would be achieved with set of physical measuring devices, such as voltmeters, accelerometers, pressure sensors or other tranducers. In medicine the set $\{\mathbf{y}\}$ is a set of measureable variables which offer an outward expression of the changes in system state. Given that the range of measurable variables may be limited in a medical situation, it is the task of the physician or diagnostician to ensure that they select a set $\{\mathbf{y}\}$ that can be used to infer the relevant values of $\{\mathbf{x}\}$.
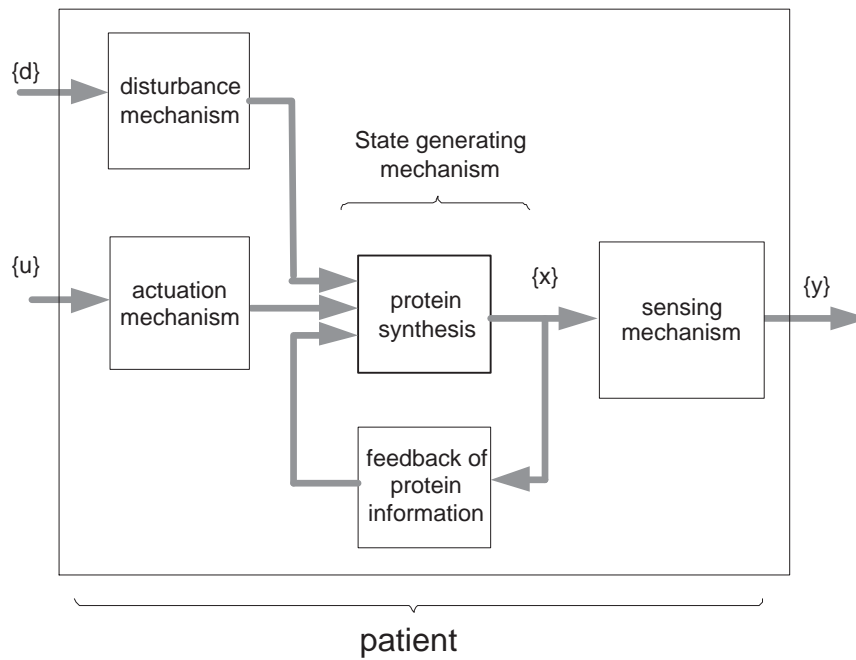


Figure 2: Input, output and state generating mechanisms.

## 1.3 Soft Sensing and State Observation

In cases where the states are needed, but are not all directly measurable, then algorithms called state observers/estimators are used to reconstruct/estimate the actual states [12]. These observers are sometimes called 'soft sensors' since they use mathematical representations and a time history of sensed variables to estimate or observe other state variables. Design of such observers typically requires mathematical models of the process in hand, including parameter values, and in medicine this is not generally feasible. Hence we assume that only the set of diagnostic indicators $\{\mathbf{y}\}$ is available, but at the same time note

the extreme importance of dynamical models in eliciting information concerning system behaviour when the corresponding state is not measurable [4].

In automated personalised medicine the aspiration is that the diagnostic indicators could be a comprehensive list of concentrations of bio–molecules in biofluids such as blood, urine, mucus, etc[5]. Ideally, if the concentrations of all bodily proteins could be measured, then diagnosis and treatment design could be made on the basis of complete knowledge of the patient's state. This complete state knowledge implies a requirement for the time histories of relevant proteins for different disease conditions. If this were to be possible then the predictive capabilities of models of disease dynamics would make a potent diagnostic tool. An important caveat in this respect is that dynamical models in technical systems are much simpler than in biology and physiology. However, given time, effort and resource it is possible to model organ function at a usefully detailed level, e.g. the virtual heart project [13] and elements of the human physiome project [14].

## 1.4 The Actuation Process and Interaction

As noted previously, the process of administering medication is the biological analogue of actuation in a technological control system. It is relevant to note here are that in technological systems we can usually be absolutely precise in applying a control signal to a system in a desired way. For example, controlling the current supplied to an electrical motor produces precisely known changes in motor torque – and nothing more. On the other hand medication will in general influence many body components in addition to the disease target. For example, pharmacologists speak of 'dirty' drugs whereas the control systems analyst would talk of highly interacting or strongly coupled actuation. This strong coupling, or multivariable, effect of a treatment upon the states is at the heart of the combinatorial treatment concept, and is this an important issue in feedback medicine. Specifically, multivariable control theory has special procedures for dealing with interaction and reducing its effects on an overall system. Thus it may be possible for multivariable feedback theory ideas to help understand how interacting treatments behave and coordinate them in some manner. We note in passing the duality between the actuation mechanism and the measurement mechanism. With the dual roles of the person who designs a medical treatment, who must understand the actuation process, and the diagnostician, who must understand the measurement process.

# 2 Issues in Conventional Feedback Medicine

If we assume that the set, $\{\mathbf{y}\}$ is comprehensive in the sense that it covers all relevant conditions, and that a (correct) diagnosis has been made, then a possible control block diagram for *feedback medicine* is shown in Figure 3. Here we assume that one treatment is prepared from a recipe of components from the set $\{\mathbf{z}\}$ specified by the treatment controller. Thus:

$$u = \sum_{i=1}^{n} b_i z_i \tag{1}$$

In the unrealistic linear case with $n$ independent outputs $\{\mathbf{y}\}$ and n independent components to the treatment $\{\mathbf{z}\}$, and laying dynamical response issues to one side for the moment, it is possible to select the combination of the inputs in equation 1 to form a medication $\{\mathbf{u}\}$ which achieves a desired diagnostic state $\{\mathbf{r}\}$ 'open loop'. That is to say with one treatment step and without the further need for feedback in the form of continued consultation with a physician (the treatment controller). In general however the patient's response to treatment is nonlinear with unknown and time varying dynamics such that the idea

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[4]An interesting question here might be, given the large number of proteins, what are the relevant subsets for particular conditions. To a degree, proteomics, aided by techniques from graph theory, attempts to address this issue. The important issue here is how to determine the sub–set of proteins (states) required a personalised feedback medicine approach to a particular disease.

[5]Metabonomics is a term used to describe the bioinformatic analysis of biofluids, see for example http://www.metabometrix.com

of a general analysis of feedback medicine is at this stage illusory. There are however some general points from control theory that can be made with for configuration shown in Figure 3, and in the following we will attempt to explore them.
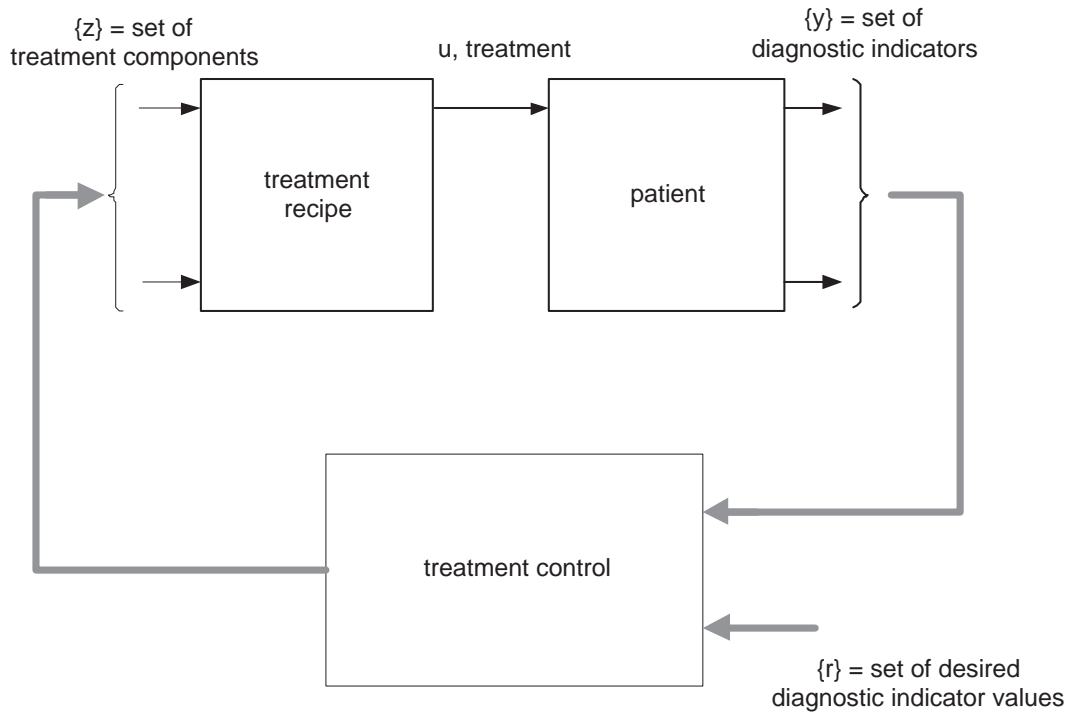


Figure 3: A feedback control interpretation for treatment of disease: 2.

## 2.1 Fixed Remedies

If only proprietary drugs and medicines are available, then the weightings on the input treatments in equation 1 can not be changed by the physician/controller, in other words $\{\mathbf{u}\}$ is largely fixed by the drug designer *a priori* with only few degrees of freedom (e.g. frequency and dosage) available to the physician. In this context, a proprietary drug is similar to a controller with fixed parameters. In medicine, as in technological feedback systems, important degrees of freedom are removed from the treatment controller by fixing the parameters. They can cause poor dynamical performance and prevent the required therapeutic state being achieved. The fact that the desired therapeutic state is a set of acceptable bands may overcome this. Specifically, it may be possible for an incorrect treatment to move the vector of diagnostic indicators into an acceptable final (steady state) region. The question of a poor dynamical response to a treatment is however an issue that that is rarely if ever discussed in medicine or biology. More specifically, there seems to be little recognition of the importance of the transient component of a patient's response to medication. We will return to this point in Section 3 of these notes.

## 2.2 Switching Treatments

If a selection of potentially suitable treatments are available, then the physician/treatment controller can try them in turn with the aim of finding a treatment that works. Switching treatments in this way creates a *hybrid control system* in which the physician changes between a set of $p$ fixed controllers (each one corresponding to a particular drug) as shown in Figure 4. The crucial point here is that hybrid (or switched mode) control systems are known to be difficult to design and analyse [15]. In particular, switching between control strategies that are themselves stable can easily lead to an unstable situation.

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This is again associated with the transient components of a controller – essentially switching between treatments before the transient elements of the first treatment have gone – causing unexpected behaviour. As an everyday example, the control systems which regulate ABS braking systems are hybrid controls with a very large number of switching rules, most of which are selected on a trial and error basis to give a stable braking control algorithm [16]. An automotive braking system is indescribably more simple than the human body. Thus it is to be expected that physicians will have difficulty deciding the efficacy of a particular treatment if they switch treatments before the effects of the previous treatments have disappeared.
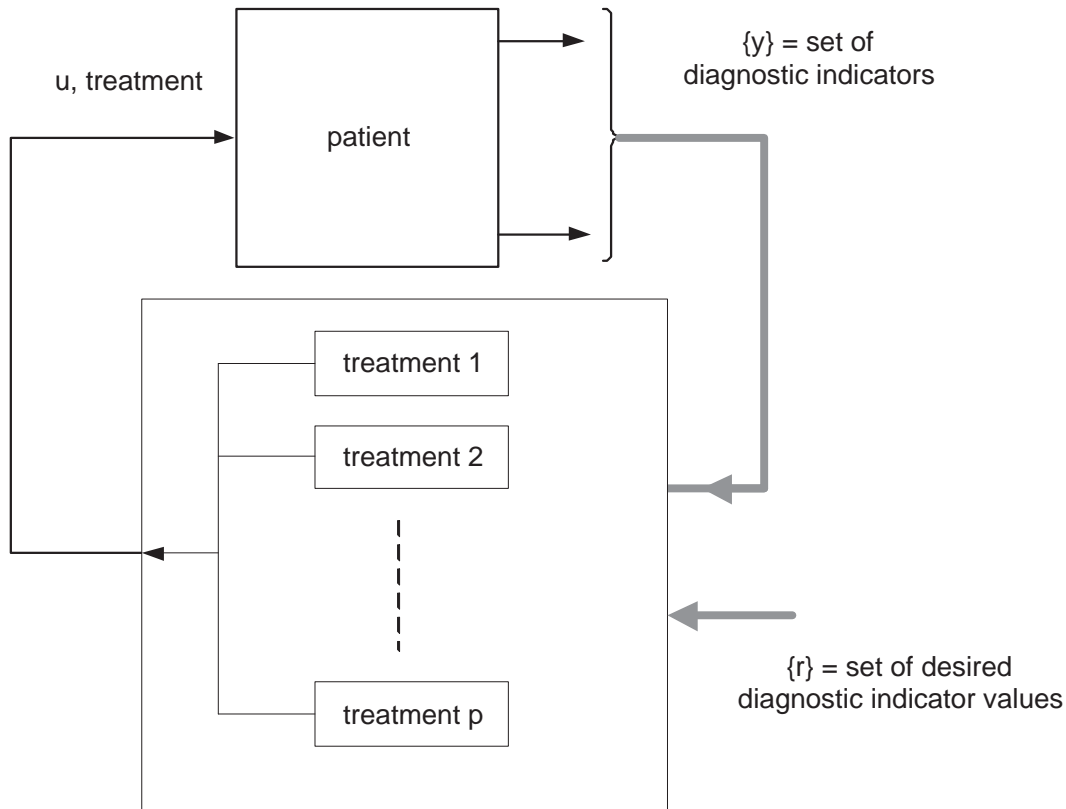


Figure 4: The 'switched treatment' of disease as a hybrid feedback control system.

## 2.3   Sampling Issues in Diagnostic Indicators

From a dynamic systems viewpoint, any control based on samples of a variable should pay close attention to errors inherent to the sampling process. One source of such errors is the limitations of the sensing instruments themselves. Another source of errors could be temporal variations in the indicator under study. In particular, if there are cyclic variations in an indicator, then taking a sample at one particular time instant may not give a representative view of the average behaviour of the indicator. In control systems this is closely related to the phenomena known as 'aliasing' and considerable attention is paid to understanding the sampling process and limiting the errors introduced by it [17]. Likewise, in control systems where the feedback is applied on the basis of time sampled information, then issues of 'intersample ripple' cannot be ignored in assessing the overall system performance [12]. In plain terms, we apply medical treatment on the basis of spot samples in time, but this may not properly control the patient outputs at times between samples.

## 2.4  Summary

In the preceding remarks we have used feedback control analogies to indicate potential limitations of conventional medicines. Enumerated they are:

1. Any medication will have a transient effect as well as the desired steady–state curative effect. By rapidly introducing medication into a patient unwanted (transient) side effects may be caused which mask a long term (e.g steady state) benefit.

2. Many if not most treatments are based upon pre–formulated drugs, which in fact introduce restrictions on the physician's ability to tailor a treatment to the needs of an individual – this is the very antithesis of personalised medicine.

3. Many if not most treatments strongly influence body components other than their target. This strong multivariable component mitigates against the use of many drugs, whereas if account were taken of the dynamics of interaction, and the variations between individuals, it may be possible to handle the interaction in a constructive way using a multivariable control paradigm.

4. Treatment is usually administered in a sampled data format by making diagnostic measurements and decisions at discrete times which may be unrelated to the dynamical response rates of the disease and treatment process. The intersample behaviour associated with slow sampling may prevent or hamper the curative influence of correct treatments.

## 3  Personalised Feedback Medicine

Now let us return to Figure 3, and reconsider it as a model for personalised medicine with the aim of makings some points about the rates at which treatments are conducted. This is relevant to the remarks in [6] and elsewhere on lessons that may be learnt from traditional medicine and the progressive introduction of treatments.

In the analysis given here, we make the simplifying assumption that the practitioner has made an apriori diagnosis [6] and selected a sufficient set of ingredients for the treatment and the initial ratio of mixing these ingredients. In the personalised feedback medicine framework, these set the initial conditions for the following time control sequence, repeated at each consultation:

1. Compare the outputs $\{\mathbf{y}\}$ with desired state $\{\mathbf{r}\}$ to form and a set of errors $\{\mathbf{e}\}$.

2. Use the error set to make an set of adjustments to the weights (amounts) of each component of the treatment.

3. Wait for next consultation and loop back to 1.

As noted in the previous section, to reduce the number of interventions required and to minimise the recovery time, a physician might well prescribe a treatment designed in to correct a disorder in one treatment session[7]. This approach is close to what is termed a 'one–step ahead' control policy in feedback control systems. One–step ahead feedback policies are known to have some drawbacks, including the fact that they demand fairly 'aggressive' control actions, with consequent side effects due to multivariable interactions.

These multivariable interactions can be illustrated in Figure 5 which is based on a system described in more detail later in Section 5. Basically, in this figure, a disease affecting the first output, $y_1$, is treated by an aggressive (high gain) feedback scenario using a combination of two independent drugs, $u_1$ and $u_2$ to return this variable to homeostasis. The drugs cause interactions with other variables, $y_2$ and $y_3$ which are returned to homeostasis by the body's internal regulatory feedback loops (via the variables $x_2$

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[6]In our reading of feedback medicine the process of diagnosis is intimately associated with the concept of state and state observer/estimator theory. We will develop this idea elsewhere in the context of maximising the possibility of correct diagnoses.

[7]In other words, the drug dosage prescribed is immediately raised to the amount calculated to combat the disorder.
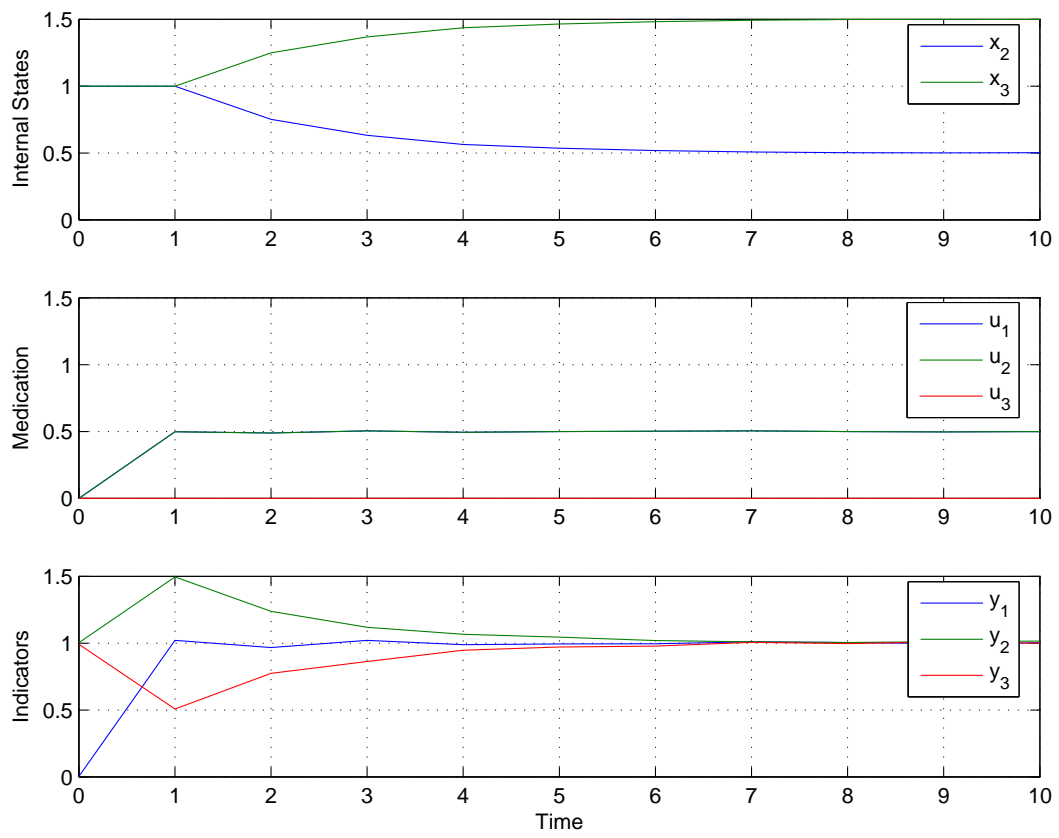
Figure 5: Simulated multivariable response with aggressive feedback control design.

and $x_3$). However, there are substantial, and potentially undesirable, transients in the variables $y_2$ and $y_3$ of approximately 50%.

Alternatively, the adjustments can be made a little more slowly to allow the body to adapt to the potentially damaging effects of the transient interactions and in a way that is consistent with the control theoretic ideas mentioned earlier. Specifically, in the 'slow change' of treatment theory, the metabolism adapts to cancel the influence of potential toxic elements of the treatment. (This is illustrated later in Figure 9 where the transient side effects are reduced to about 15% albeit at the cost of an approximate doubling of the time before complete regulation is achieved.)

Likewise, an additional consideration could be that the slow change in medication will avoid de–stabilising the complex interacting multivariable system that is the human body. Essentially, in a feedback loop the dynamics of the body in processing medication interact with the dynamics of the treatment regime in ways that can be de–stabilising. Thus traditional medicine may have, in one of its aspects, empirically discovered ways of designing a stabilising feedback controller. We explore this possibility and others in the following sections using simplified models of the disease process.

Thus we would argue that there is a trade–off in the treatment prescribed between on the one hand minimising recovery times (and simultaneously reducing the number of consultations required) versus reducing transient interactions and their associated problems with transient side effects and potential destabilisation.

The idea of feedback medicine is to bring control systems theory to health be control of 'exogenous' signals (drugs and treatments etc). The internal feedbacks associated with Homeostatis and Allostatsis can be referred to as 'endogenous' control. What the example demonstrated is that the exogenously introduced controllers can "fight" the endogenous controls.

# 4   Coordinated Treatment: An Illustrative Example

Consider a framework in which we have two different drugs available, A and B, for the treatment of a single disease. We also suppose that on average, across the population, both drugs have a similar affect on the disease. Also suppose that the disease has been correctly diagnosed with a single diagnostic indicator to be used for monitoring and regulation purposes. There are therefore three main strategies for treatment: (i) use drug A (only); (ii) use drug B (only); or (iii) use a combination of both drugs A and B. This latter strategy we will refer to as 'Coordinated Treatment' – which is equivalent to the combinatorial treatment terminology of [6]. This coordinated treatment option, although more complicated to consider, does seem to offer some advantages that we illustrate by a simple *in silico* example.

To simplify the example, we consider one main state variable, $x$ which can be directly measured. We denote the value of the state at each test time (for example weekly tests), $k = 0, 1, 2...$ by $x_k$, and the drug input(s) at each time by $u_{Ak}$ and $u_{Bk}$. If for a given patient, the two drugs, A and B, have sensitivities $s_A$ and $s_B$ (respectively)[8], then we describe a very simple[9] form of patient behaviour by:

$$x_{k+1} = s_A \times u_{Ak} + s_B \times u_{Bk} \qquad (2)$$

The target value for $x$ is taken to be 100%, but we assume that the patient is in a diseased state wherein without intervention, $x$ becomes zero within one time interval. Therefore, some form of drug intervention is needed and the treatment should be designed to at least return $x_k$ to within 50% of the target value. We shall use the symbol $e_k$ to denote the deviation of $x_k$ from the target value, that is $e_k = x_k - 1$.

## 4.1   Treatment Regimes

We consider two main treatment regimes. In each case, the physician monitors, at (say) a weekly interval, the indicator, until either: (a) the physician makes a decision to discontinue treatment (for example if

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[8]Here we define sensitivity to be the response size per unit quantity of a drug.

[9]In this example, we are assuming simple linear independent effects from the drugs, and that the natural residence time of the state is much smaller than the sampling time.

there is a negative response to the treatment); or (b) the indicator is within +50% to +150% in which case the therapy is deemed to have succeeded, and the current drug dosage is maintained.

Until a treatment regime is completed, the physician changes the drug dosage by an amount proportional[10] to the error between the actual, and target indicator value (100%). In this example, we take the proportionality as $1/2$, which corresponds to a cautious approach to treatment, trying to avoid (if possible) over medication.

### 4.1.1 Single Drug Prescription

Suppose that the treatment regime is the use of a single drug, (since the problem is symmetric we chose A), which is adjusted according to the rule that the drug input is decreased by an amount proportional (in this case 50%) to the deviation of the indicator from the target. This can be described by the rule:

$$
\begin{aligned}
uA_k &= uA_{k-1} - 0.5 \times (x_k - 1) \\
uB_k &= 0
\end{aligned}
\tag{3}
$$

Combining equations (2) and (3) with a little algebra leads to:

$$
e_{k+1} = \left(1 - \frac{s_A}{2}\right) e_k
\tag{4}
$$

### 4.1.2 Combined Drug Prescription

The second treatment regime we consider is the use of a equal doses of both Drug A and Drug B. The total dosage is adjusted according to the rule that the total drug input is decreased by an amount proportional (in this case 50%) to the deviation of the indicator from the target. This can be described by the rule:

$$
\begin{aligned}
uA_k + uB_k &= uA_{k-1} + uB_{k-1} - 0.5 \times e_k \\
uB_k &= uA_k
\end{aligned}
\tag{5}
$$

Combining equations (2) and (5) with a little algebra leads to:

$$
e_{k+1} = \left(1 - \frac{s_A + s_B}{4}\right) e_k
\tag{6}
$$

We now turn to consider simple measures of the probability of treatment success for variable patient responses to the drugs.

## 4.2 Treatment Success for Variable Patients

Of course, if an individual patient responds as expected to the drugs according to the average of the population $s_A = s_B = 1.0$, treatment will be 'successful' in a single step, whereby the indicator is (just) within the acceptable range. However, if we allow for inevitable variability in an individual patient's sensitivity to the drugs, things are slightly more complicated. In fact, for some patients, the treatment may not lead to a successful outcome at all, namely, where the treatment strategy chosen will never lead to a situation where the indicator is within the target range.

The time update equation (4) shows that provided $\left|1 - \frac{s_A}{2}\right| < 1$ at each time step, the size of $e_k$ will decrease (exponentially) and therefore the treatment will eventually be successful (at least in sufficient time). On the other hand, if $\left|1 - \frac{s_A}{2}\right| > 1$ the treatment regime will cause the indicator to diverge from the target value. The main reason that this might occur is if $s_A < 0$, that is the selected drug A has a negative impact on the particular patient. Note that it is also possible that divergence could occur if $s_A$ is positive and much larger than expected, i.e. hyper sensitivity in the patient. For simplicity, we ignore this case since this is not a practical scenario since: (i) the physician would almost certainly notice, in the

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[10]Note that here we ignore learning and adaptation in the physician's behaviour. This would be harder to model, but may lead to improved treatment completion times.

response of the indicator, the patient's hyper-sensitivity, and therefore change the treatment strategy; (ii) If the strategy were not changed, then it can be shown that within a few time steps, negative amounts of drug would be prescribed. This is clearly impractical and the simple model in (3) would break down.

Under these assumptions, it is clear that provided $s_A > 0$ then eventually, treatment with drug A only will succeed. Similarly, from (4) it can be shown that treatment will succeed within $k$ steps provided $s_A > 2\left(1 - 2^{-1/k}\right)$. So for example, if we wish to examine when successful treatment can be expected within $k = 4$ time periods, we need $s_A > 0.3182$.

Note that in the case of the coordinated treatment, the situation is the same except that in all cases now, we replace the single sensitivity to an individual drug $s_A$ by the patient's average sensitivity to the two drugs $\frac{1}{2}(s_A + s_B)$. For example therefore, the coordinated treatment will be eventually successful if $s_A + s_B > 0$ and the treatment will be successful within $n = 4$ time periods if $s_A + s_B > 0.6364$.

To illustrate the potential benefits of the drug treatment regime of Subsection 4.1.2 we perform some simulations and analysis on a simplified scenario. Suppose that the patients' sensitivities to either drug A or drug B are independent of each other, and that in each case, 95% of patients will respond positively to the drug. If we assume a normal distribution for the patient sensitivities, then both $s_A$ and $s_B$ will have mean value of 1 and standard deviation of 0.6. However, under the assumption that they are independent, the distribution of the average sensitivities is also a normal distribution with mean 1, and standard deviation $0.6/\sqrt{2} = 0.424$. This somewhat modest decrease in variability give a considerable reduction in failure rates for the treatment. In fact, the 5% failure rate for a single drug, under this model, would reduce to 1%. Similarly, the rate of failures within four time cycles would reduce from 13% for the single drug treatment to 5% for the combined drug treatment.

Figure 6 illustrates this behaviour by showing the combination of sensitivities based on a random selection of 1000 patients according to the distributions described above. It also shows the dividing lines of where different treatment regimes will be effective or not, and where boundaries of where the different treatment regimes could be expected to complete within four time cycles.

## 4.3 Side Effects

Another advantage of the treatment regime suggested in Subsection 4.1.2 that might be predicted by a dynamic systems approach is a reduction, in some sense, of the side effects of the medication. In the simplest case, we ignore dynamic affects and patient variability, and look at the treatment using different combinations of drugs. So in the ideal case, where $s_a = s_B = 1$, then we can achieve the desired response at the indicator of $x = 1$ by taking any combination of drugs that satisfies:

$$u_A + u_B = 1; u_A \geq 0; u_B \geq 0 \tag{7}$$

There are a number of different ways of measuring the overall side effects due to independent drugs. The simplest measure[11] $(m)$ might be the total drug dose: $m_1 = u_A + u_B$. We would argue that a more realistic measure might be either the peak drug dose $m_\infty = max\{u_A, u_B\}$ or the root mean square drug dose $m_2 = \sqrt{u_A^2 + u_B^2}$. Both of these measures better capture the qualitative features of many side affects whereby small deviations can be compensated for by the body's natural regulatory systems, but where larger deviations may exceed the body's ability to reject this side effect.

Note that in the example we are considering, as far as side effects are concerned:

- For any of the side effect measures $m_1$, $m_2$ or $m_\infty$ no strategy that achieves the required regulation, (7), does better than the coordinated treatment $u_A = u_B = 0.5$

- For either of the side effect measures $m_2$ or $m_\infty$ the strategy that 'minimises' side effects whilst achieving regulation,(7), is the coordinated treatment $u_A = u_B = 0.5$

Note that this strategy can be thought of as application of the feedback control concept of controller direction 'alignment' (see for example [18] where this is discussed for the dual problem of single input two output systems). Broadly speaking, this concept can be interpreted as saying that all other things

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[11]From a mathematical viewpoint, the measures proposed are different 'norms' that might be used to quantify the overall size of the drug dose vector $[u_A, u_B]$.
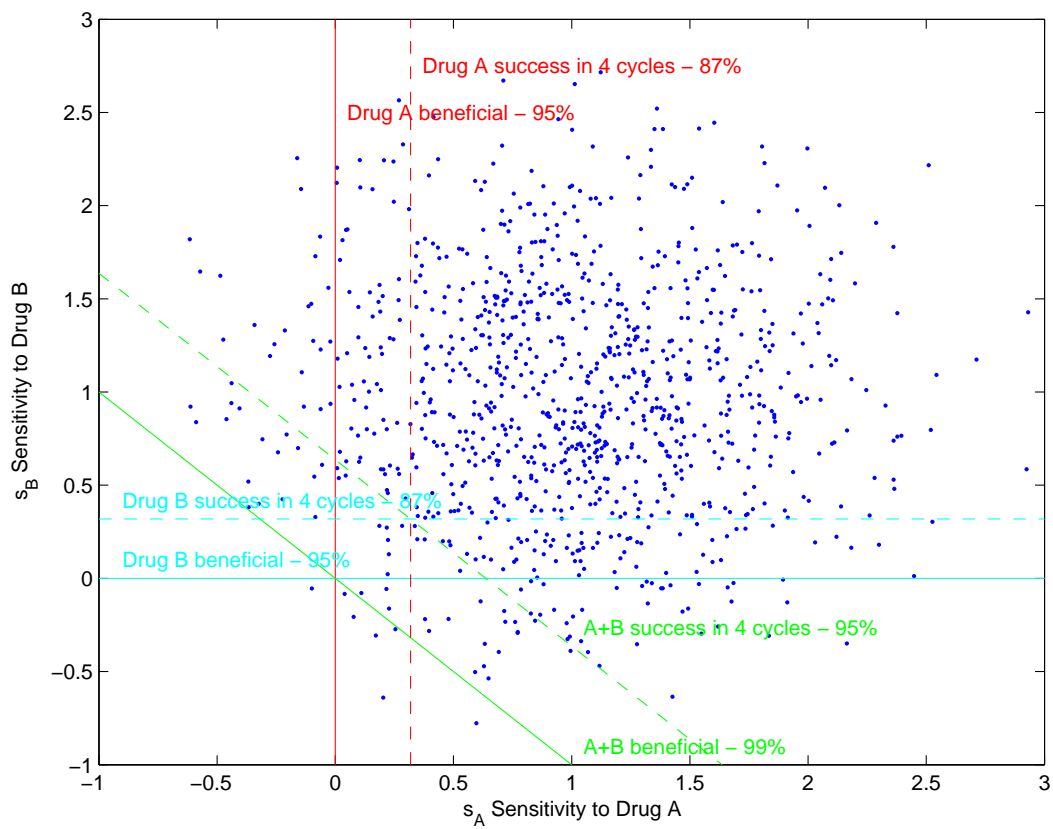
Figure 6: Simulated patient sensitivities for two equally effective drugs, A and B, together with coordinated treatment $\frac{1}{2}A + \frac{1}{2}B$.

being equal, to minimise the required control responses, and also to improve robustness, the relative weightings on the combination of treatment components (i.e. inputs) used should approximately reflect the responsiveness of the patient to each individual treatment component. It is also known from the control literature that this will in general produce a more robust control algorithm than strategies that don't respect this suggestion.

# 5    Side Effects and (partial) Homeostasis

In this section, we wish to illustrate some side effects that can occur when trying to regulate a multivariable system. We consider the simple case of a system (modelling in a crude way homeostasis) with 3 important variables, each of which we assume can be measured. We denote these variables by $y_1$, $y_2$ and $y_3$ respectively. Each of these variables has two main influences - a contribution due to external inputs (i.e. medication) and internal biological regulator processes. The internal regulatory processes have state variables that we denote by $x_1$, $x_2$ and $x_3$ respectively. We also suppose that the three drug components available, $u_1$, $u_2$ and $u_3$ have interactions between the different variables given by the matrix $M_u$. We then take the simple (static) mathematical model:

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = M_u \times \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} + \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} \tag{8}$$

We take, for illustration, $M_u = \begin{bmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & -1 & -1 \end{bmatrix}$ whereby, the first drug component has a positive effect on indicators 1 and 2; the second drug component has a positive effect on indicators 1 and 3; and the third drug suppresses (i.e. has a negative effect) on indicators 2 and 3. In a healthy individual, we assume that biological regulatory processes add dynamics to achieve perfect adaptation through integral feedback control [19]. We describe these processes by the differential equation:

$$\frac{d}{dt}\left(x_i(t)\right) = r_{bi} - y_i(t); i = 1..3 \tag{9}$$

where $r_{bi}$ are internal biological references for which (9) will generate actions through negative feedback in an attempt to achieve Homeostasis, that is, $y_i(t) \rightarrow r_{bi}$.

In our simple example, we take each of the biological references to be unity. We also consider a case where disease affects the first set of state and output variables and forces, instead of (9), the first state component to obey $x_1 = 0$. Note that throughout this section, we constrain all variables to take non-negative values.

We now wish to consider two different approaches to medical intervention (external regulation) of such a patient.

## 5.1    External 'Perfect' Regulation of All Variables

In the first approach to medical intervention, suppose the physician, knowing that there are 3 drugs available, and 3 diagnostic indicators, tries to adapt and regulate all variables to reference values that we denote by $r_{pi} : i = 1..3$. Ideally, these reference values should be equal to the internal biological reference values, $r_{bi} : i = 1..3$. Also, let us suppose that the physician knows of the drug interactions, and the matrix $M_u$ and therefore is able to compensate for these interactions in the proposed treatment regime using the inverse $M_u^{-1} = 0.5 \begin{bmatrix} 1 & 1 & 1 \\ 1 & -1 & -1 \\ -1 & 1 & -1 \end{bmatrix}$. The treatment regime proposed[12] is then described by

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[12]Technically, the multiplication by $M_u^{-1}$ should be after the controller, not before, however, because the control proposed (after compensation) is identical in all channels, this makes no difference to the analysis in this case.

the difference equation[13]:

$$\begin{bmatrix} u_{1\,k+1} \\ u_{2\,k+1} \\ u_{3\,k+1} \end{bmatrix} = \begin{bmatrix} u_{1k} \\ u_{2k} \\ u_{3k} \end{bmatrix} + 0.5 \times M_u^{-1} \begin{bmatrix} r_{p1} - y_{1k} \\ r_{p2} - y_{2k} \\ r_{p3} - y_{3k} \end{bmatrix} \qquad (10)$$

In this situation, and in the ideal case where the biological reference values, $r_{bi}$ are identical to the physician's reference values $r_{pi}$ we obtain simulation results as given in Figure 7.
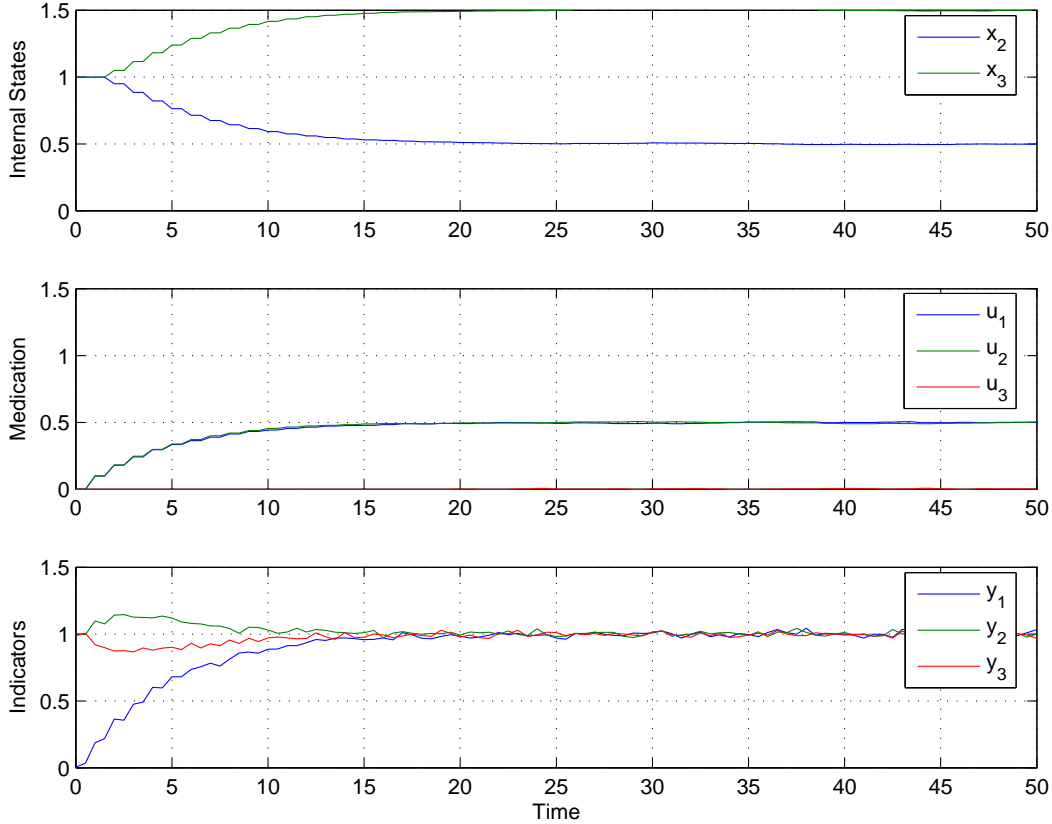


Figure 7: Simulated patient transient response to treatment with external regulation of all variables to the exact biological values.

In Figure 7, the responses are all well behaved, with the medication fairly rapidly converging to values that give all variables at their target values of 1.0.

However, if we repeat the simulations, except in this case with a slight (10%) deviation between the internal biological reference values $r_{bi}$ and the physician's external reference values $r_{pi}$. In this case, we obtain the simulation results shown in Figure 8.

From this figure we see that at least initially (up to about 5 to 10 time samples), the response is quite close to that shown earlier in Figure 7. However, after this time, a continual drift, ending in quite substantial deviations can be seen.

This drift can be observed in both medication levels, and internal states of the patient, but is largely unobservable in the behaviour of the diagnostic indicators. In this simulation example, the drift continues until some of the regulators are so far from normal conditions that they saturate and they themselves are

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[13]Note that this difference equation is qualitatively very similar to the differential equation (9) except that in this case, the physician's interventions can only be altered at a discrete set of times, which are indexed by the variable 'k' in (10).
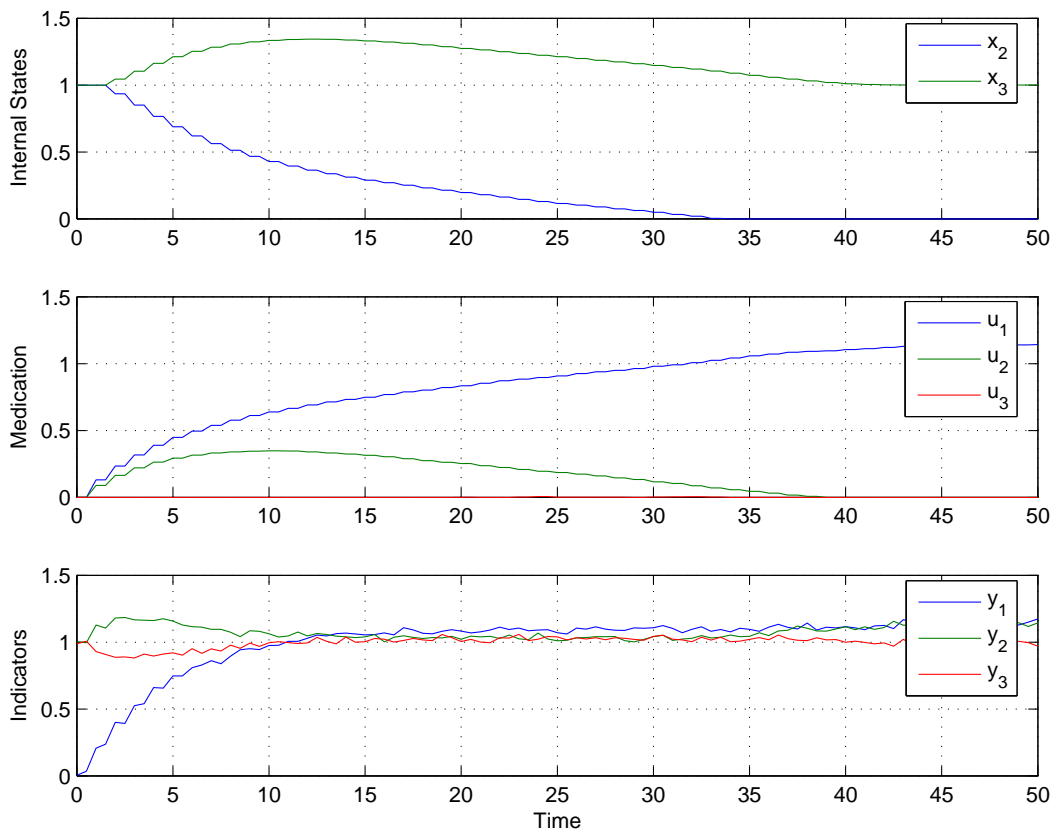
Figure 8: Simulated patient transient response to treatment with external regulation of all variables with 10% deviation between internal biological and external reference values.

no longer capable of maintaining homeostasis. In this particular example, the regulators that saturate are:

- Internal regulation of the 3rd state, $x_3$ which reaches zero at approximately the 34th sample, and thereafter is clamped at zero.

- External regulation via administration of the 2nd drug component, $u_2$, which reaches zero a short time later, and thereafter is clamped at zero.

In this case, we see that the internal and external regulatory loops are 'fighting' each other, namely, they are both trying to achieve perfect adaptation, but to slightly different reference values. This results in the undesirable behaviour leading to much higher than necessary drug dosages (in some components of the drug), and saturation of internal biological regulatory mechanisms.

From a dynamical systems point of view, it can be shown that the patient model described above, gives a transfer function that has two (steady state) transmission zeros, in other words, the steady state response patient response drops from rank 3 (as might normally be considered for a three output system) by 2 (due to the transmission zeros) to a rank 1 matrix. It is well known in dynamical systems, that to close $m$ integral feedback loops (i.e. perfect adaptation mechanisms) around a plant, the steady state transfer matrix should have rank no less than $m$ or else there will necessarily be marginally stable hidden modes (i.e. hard to observe drifting modes) in the response. This explains the poor behaviour exhibited in this example.

Note that this example is not an isolated case. Indeed, any time that we have measurement of a variable for which there is an internal regulatory loop that achieves perfect regulation, it necessarily follows that there will be a transmission zero to this variable, and external perfect adaptation should not normally also be employed for this variable.

## 5.2 Coordinated Regulation of a Single Variable

An alternative approach, suggested by dynamical systems theory, would be to allow integral action ('perfect adaptation') of a single variable only, namely, $y_1$ for which the biological regulatory system is inoperative.

In this case, we consider a single dynamic variable, $v_k$ which we update by the equation:

$$v_{k+1} = v_k + 0.5 \times (r_{p1} - y_{1k}) \tag{11}$$

(11) together with the control action equation (suggested in view of the discussions in Section 4.1.2):

$$u_k = \begin{bmatrix} 0.5 \\ 0.5 \\ 0 \end{bmatrix} v_k \tag{12}$$

Using the treatment regime described by (12), (11) (in place of the (10) ) we obtain the simulated responses given in Figure 9 even with discrepancies between the internal biological reference variable (which in this case is deactivated) $r_{b1}$ and the external reference $r_{p1}$.

Note that in this case the response is close to the ideal case, with little use of drugs and without saturating any of the natural feedback mechanisms.

## 5.3 Remarks on 'Linear' Systems

Our discussions here are in some cases based on what might be termed *independent responsiveness* in a system. In a feedback control systems context, this is often termed *linearity*, however we believe this term has an alternate usage in other disciplines where linearity might be taken to imply 'simple', 'smooth', easily predictable behaviour. In particular, from a feedback control systems perspective, 'linear' systems permit quite complex behaviours, as illustrated in Figure 10.

The feedback control systems of linearity or *independent responsiveness* can be defined by the two key properties of: *(i) proportionate response* – which loosely speaking means that if an action produces a
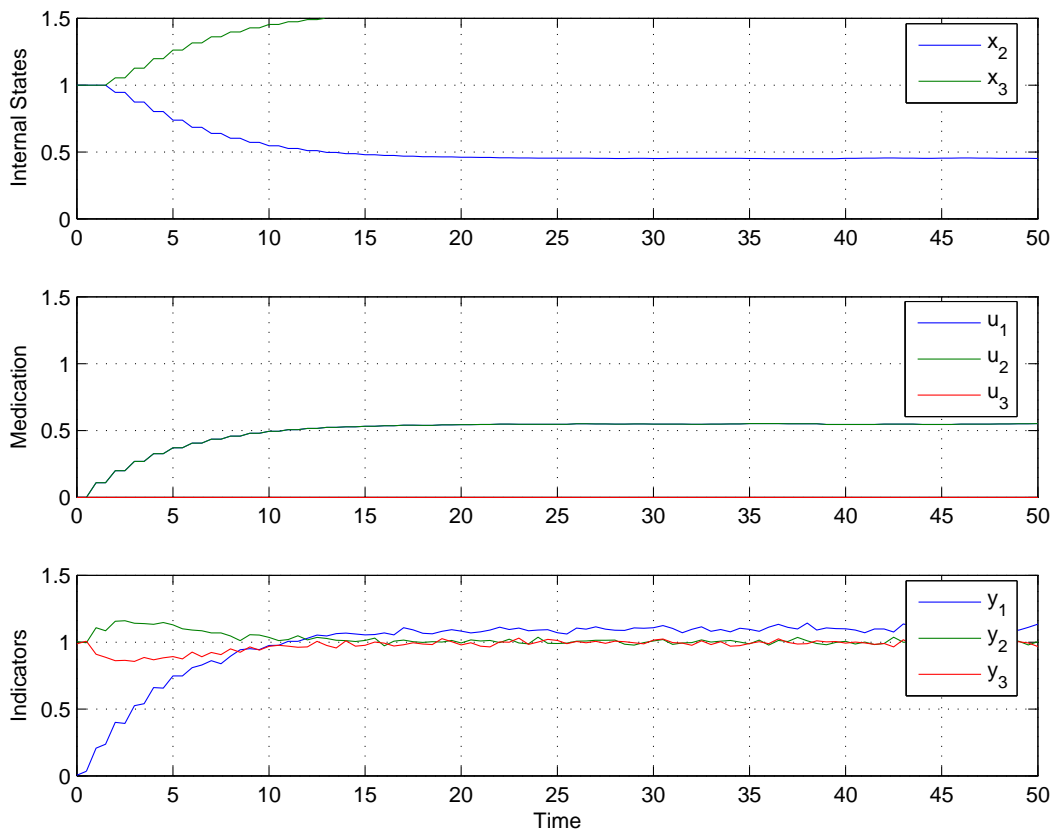
Figure 9: Simulated patient transient response to treatment with external regulation of first variable only, allowing for 10% error in reference values.
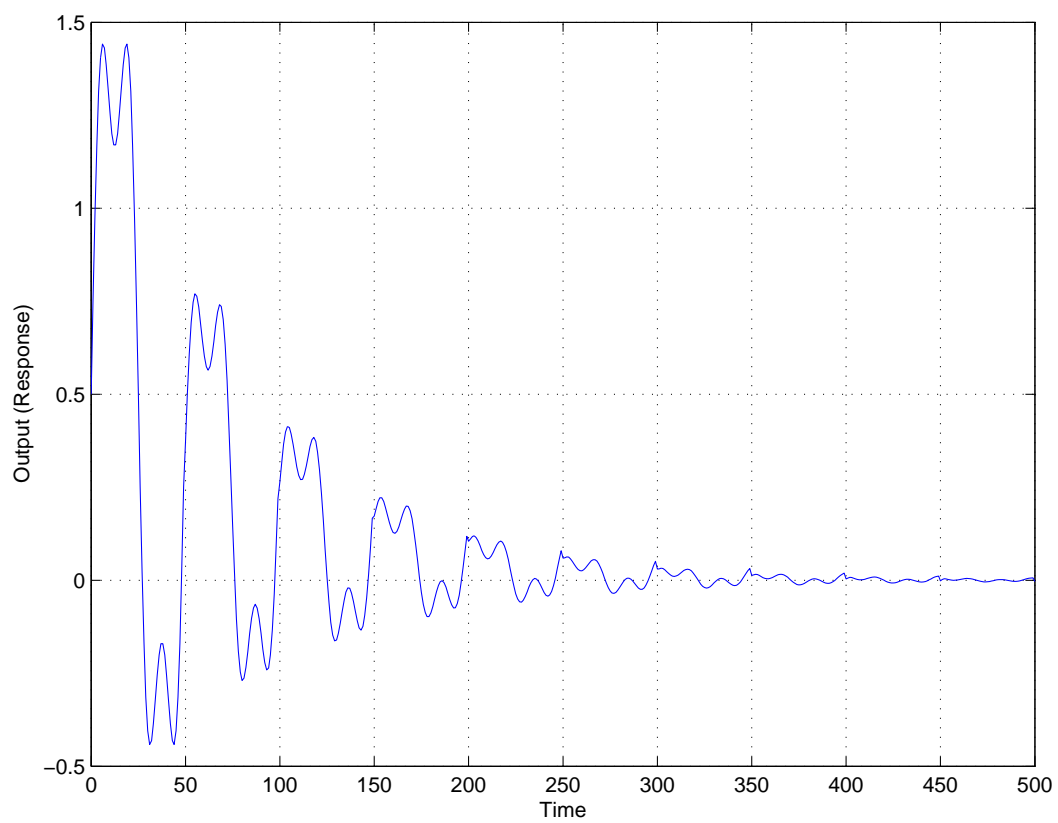
Figure 10: Example of a complicated response arising from a purely 'linear' system.

certain response, an increased action will produce an increased response[14]. *(ii) cumulative affects* – which loosely means that the result of combined actions can be reasonably predicted simply by combining[15] the results of individual actions.

Whilst it is certainly true that there are heavily dependent responses (non–linearities) in the dynamics of biomedical systems, we argue that a study based on linearisation is an appropriate first step. Our primary reasons for this are that the linear case is frequently a useful approximation of a non–linear system; and, that the theory and understanding of linear dynamic systems is far more straightforward and developed than the equivalent theory for non–linear systems. Furthermore, the framework we propose is aimed at keeping homeostasis, and avoiding large perturbations to this where nonlinear affects will be more pronounced. A more extensive study could include extra nonlinear features such as: (i) Saturation of variables (i.e. in several cases, it may not be possible, or there may be unacceptable side effects of variables exceeding certain ranges); (ii) Complicated variable interactions (e.g. the use of drugs which on their own are acceptable, but who's combined use may be contra–indicated; or conversely, drugs which on their own have a small therapeutic effect, but which combine in a "strongly" synergistic manner).

# 6    What Next?

In these notes we ask whether knowledge from feedback control theory can be employed to make meaningful statements about personalised and combinatorial medicine. To do this we have made assumptions and simplifications which maybe inappropriate. Likewise or examples and conclusions may be obvious to biologists and medical researchers. In this spirit, we invite scientific feedback and comments on the potential relevance of the feedback medicine concept and the examples used in this document.

# Acknowledgements

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[14]Technically, the increased response should be proportionate to the increase in action

[15]Mathematically, the response to a sum of actions should be exactly the sum of the individual responses to each action.

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{x} = system state

patient

measurement
mechanism

{y} = set of
diagnostic indicators